Diabetes Mellitus: Screening and Diagnosis

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Diabetes mellitus is one of the most common diagnoses made by family physicians. Uncontrolled diabetes can lead to blindness, limb amputation, kidney failure, and vascular and heart disease. Screening patients before signs and symptoms develop leads to earlier diagnosis and treatment, but may not reduce rates of end-organ damage. Randomized trials show that screening for type 2 diabetes does not reduce mortality after 10 years, although some data suggest mortality benefits after 23 to 30 years. Lifestyle and pharmacologic interventions decrease progression to diabetes in patients with impaired fasting glucose or impaired glucose tolerance. Screening for type 1 diabetes is not recommended. The U.S. Preventive Services Task Force recommends screening for abnormal blood glucose and type 2 diabetes in adults 40 to 70 years of age who are overweight or obese, and repeating testing every three years if results are normal. Individuals at higher risk should be considered for earlier and more frequent screening. The American Diabetes Association recommends screening for type 2 diabetes annually in patients 45 years and older, or in patients younger than 45 years with major risk factors. The diagnosis can be made with a fasting plasma glucose level of 126 mg per dL or greater; an A1C level of 6.5% or greater; a random plasma glucose level of 200 mg per dL or greater; or a 75-g two-hour oral glucose tolerance test with a plasma glucose level of 200 mg per dL or greater. Results should be confirmed with repeat testing on a subsequent day; however, a single random plasma glucose level of 200 mg per dL or greater with typical signs and symptoms of hyperglycemia likely indicates diabetes. Additional testing to determine the etiology of diabetes is not routinely recommended. (Am Fam Physician. 2016;93(2):103-109. Copyright © 2016 American Academy of Family Physicians.)

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Uncontrolled diabetes can lead to blindness, limb amputation, kidney failure, vascular disease, and heart disease. It is estimated that in the next 20 years, the number of persons with type 2 diabetes in the United States will reach 44 million, approximately double the current prevalence. Diabetes likely will continue to be one of the most common diagnoses made by family physicians. Diagnostic testing should be performed in individuals with a clinical history indicative of diabetes. Symptoms that should prompt consideration of diabetes include polyuria, polydipsia, fatigue, blurry vision, weight loss, poor wound healing, numbness, and tingling. This article focuses on screening and diagnosis of diabetes in asymptomatic patients.

Classifying Diabetes

Type 1 diabetes is caused by autoimmune destruction of the islet cells of the pancreas, and onset is typically in childhood. Type 2 diabetes is caused by insulin resistance and is more common in patients who are obese. Previously thought to primarily affect adults, type 2 diabetes is now being diagnosed more often in children and adolescents with obesity. End-organ damage and complications are similar in both types of diabetes.

TYPE 1 DIABETES

Screening for type 1 diabetes is not recommended for the following reasons: patients typically present with an acute onset of symptoms, no established cutoff value is available for antibody tests, no accepted
treatment exists for patients who are asymptomatic, and no medication is available to prevent the disease in persons genetically predisposed to type 1 diabetes.5,6

TYPE 2 DIABETES

Screening is recommended for type 2 diabetes because reliable tests are available, and lifestyle changes and medications reduce progression and adverse sequelae of the disease, even in persons who are initially asymptomatic.7,8

Although screening for type 2 diabetes does not improve mortality after 10 years of follow-up,9,10 studies show that lifestyle and pharmacologic interventions in patients with impaired glucose tolerance and impaired fasting glucose can delay development of type 2 diabetes,11 with some studies showing greater effectiveness with lifestyle changes.11,13 Other studies suggest screening may begin to show benefits in mortality after 23 to 30 years.14,15 One randomized trial showed a statistically significant reduction in the incidence of all-cause and cardiovascular mortality in patients with impaired glucose tolerance treated with lifestyle modifications, although only after 23 years of follow-up (not found at 20-year evaluation). This study was conducted in China and may not be applicable to a U.S. population.15

Who Should Be Screened

NONPREGNANT ADULTS

Multiple professional organizations have published screening recommendations for type 2 diabetes, although slight differences exist (Table 1).8,16-20 The U.S. Preventive Services Task Force (USPSTF) recently updated recommendations and suggests screening individuals 40 to 70 years of age who are overweight or obese. Persons with abnormal results should be referred for intensive behavioral counseling interventions focusing on physical activity and a healthy diet. Clinicians should consider screening certain individuals at higher risk.7,8 The USPSTF relied on evidence from randomized trials to identify populations who would be most likely to benefit from screening. Based on cohort studies, the American Diabetes Association (ADA) recommends screening a broader population based on risk, including all adults 45 years or older regardless of risk, and includes screening for prediabetes in the guidelines.21 There are multiple risk prediction calculators available,22-24 although most prediction models overestimate diabetes risk.5 However, the Canadian Task Force on Preventive Health Care recommends using one of two validated risk questionnaires to help determine who should be screened.18

Based on expert consensus, current guidelines recommend annual screening in high-risk patients or those with results nearing diagnostic thresholds. For average-risk patients with normal screening results, testing can be repeated every three years.8,17,25

PREGNANT WOMEN

Hyperglycemia increases the risk of congenital malformations and intrauterine fetal death. Women with gestational diabetes mellitus (GDM) who have fasting hyperglycemia have a three- to fourfold increased risk of infant malformations.26,27 The goal of screening is to reduce maternal and fetal complications such as pre-eclampsia, cesarean delivery, congenital malformations, macrosomia (and later childhood/adolescent overweight), shoulder dystocia, nerve palsy, bone fracture, jaundice, and infant death.26,28-30

The ADA advises screening pregnant women in their first trimester if they have risk factors for developing type 2 diabetes (Table 1)8,16-20 or GDM, including obesity, advanced maternal age (older than 35 years), history of GDM, family history of diabetes, and belonging to a high-risk ethnic group.27 The American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention agree with this recommendation.31,32 However, the American Academy of Family Physicians and the USPSTF recommend screening for GDM only after 24 weeks’ gestation.29,33,34

Screening for GDM should be performed using a two-step 50-g nonfasting oral glucose challenge test; if the
result is positive, this is followed by a diagnostic 100-g fasting oral glucose tolerance test. Further information about screening and diagnosis of GDM is available in a previous article in *American Family Physician* (http://www.aafp.org/afp/2015/0401/p460.html).

**CHILDREN**

The ADA recommends screening children and adolescents 18 years and younger who are overweight (i.e., body mass index greater than 85th percentile for age and sex, weight for height greater than 85th percentile, or weight
greater than 120% of ideal [50th percentile] for height) and who have any two of the following risk factors: history of type 2 diabetes in a first- or second-degree relative, belonging to a high-risk ethnic group (Table 18,16-20), acanthosis nigricans, hypertension, hyperlipidemia, or polycystic ovary syndrome.35 The American Academy of Pediatrics and the ADA recommend screening at-risk patients every two years starting at 10 years of age, or at onset of puberty if before 10 years of age.36,37

OLDER ADULTS
Although more than 50% of older adults have prediabetes, and older adults in general are at higher risk of prediabetes and type 2 diabetes, the benefits of screening depend on whether treatment would improve the patient’s overall quality of life or life expectancy.38 No organizations currently recommend routine screening in geriatric patients, although the ADA does support the consideration of screening at-risk patients every two years starting at 10 years of age, or at onset of puberty if before 10 years of age.36,37

Diagnostic Testing
The diagnosis of diabetes can be made when classic signs and symptoms of hyperglycemia are associated with a single random plasma glucose measurement of 200 mg per dL (11.1 mmol per L) or greater. Alternatively, the diagnosis can be made with an A1C level of 6.5% or greater, a fasting plasma glucose level of 126 mg per dL (7.0 mmol per L) or greater, or a two-hour, plasma glucose level of 200 mg per dL (11.1 mmol per L) during an OGTT; test should be performed as described by the World Health Organization using a 75-g anhydrous glucose load dissolved in water or Random plasma glucose ≥ 200 mg per dL with classic symptoms of hyperglycemia

Table 2. Interpretation of Diabetes Mellitus Diagnostic Tests

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Prediabetes or increased risk of diabetes</td>
<td>Impaired fasting plasma glucose: fasting plasma glucose = 100 to 125 mg per dL (5.6 to 6.9 mmol per L) or Impaired glucose tolerance: two-hour plasma glucose in the 75-g OGTT = 140 to 199 mg per dL (7.8 to 11.0 mmol per L) or A1C 5.7% to 6.4%</td>
<td>Risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range</td>
</tr>
<tr>
<td>Diabetes</td>
<td>A1C ≥ 6.5%; test should be performed in a laboratory using a National Glycohemoglobin Standardization Program–certified method and standardized to the Diabetes Control and Complications Trial reference assay or Fasting plasma glucose ≥ 126 mg per dL (7.0 mmol per L); fasting refers to no caloric intake for at least eight hours or Two-hour plasma glucose ≥ 200 mg per dL (11.1 mmol per L) during an OGTT; test should be performed as described by the World Health Organization using a 75-g anhydrous glucose load dissolved in water or Random plasma glucose ≥ 200 mg per dL with classic symptoms of hyperglycemia</td>
<td>In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing</td>
</tr>
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OGTT = oral glucose tolerance test.
and ethnic groups.\textsuperscript{44–48} Point-of-care A1C measurements are not recommended for the diagnosis of diabetes.\textsuperscript{2,17} A1C testing should be performed in a laboratory using a method certified by the National Glycohemoglobin Standardization Program and consistent with the Diabetes Control and Complications Trial reference assay.

**FASTING PLASMA GLUCOSE**

The National Health and Nutrition Examination Survey data indicate that fasting plasma glucose values may identify as many as one-third more undiagnosed cases of diabetes compared with A1C levels.\textsuperscript{2,17,49} Fasting plasma glucose measurement should be obtained by a venous blood draw; elevated glucometer or continuous glucose monitor measurements are not considered diagnostic.\textsuperscript{17}

**SPECIAL TESTS**

Increasingly, diabetes is being recognized as a spectrum of disorders including type 1 diabetes, type 2 diabetes, GDM, prediabetes, neonatal diabetes, maturity-onset diabetes of youth, and latent autoimmune diabetes in the adult. Overlap exists in the underlying etiology of these disorders.\textsuperscript{2,5,16,30–53} Autoimmune markers usually present in patients with type 1 diabetes include autoantibodies to one or more of the following: islet cells, insulin, glutamic acid decarboxylase, insulinoma-associated antigen-2, and zinc transporter (Table 4\textsuperscript{17,50–53}). Patients with idiopathic type 1 diabetes have no autoantibodies, and some patients with latent autoimmune diabetes in the adult or type 2 diabetes may have certain autoantibodies present making these tests less specific.\textsuperscript{5} Despite these concerns, the American Association of Clinical Endocrinologists recommend routine confirmation of type 1 diabetes using autoantibody testing.\textsuperscript{16} Additional research is required to determine whether further testing to classify the etiology of diabetes improves patient outcomes. In the meantime,
additional testing is not routinely recommended.

Data Sources: A PubMed search was completed using the key terms diabetes mellitus, diabetes mellitus type 2, screening for diabetes mellitus, gestational diabetes, geriatrics, elderly, and pediatrics. The search included meta-analyses and reviews. Also searched were Essential Evidence Plus, the websites of the American Diabetes Association, the U.S. Preventive Services Task Force, the American Academy of Family Physicians, and the American Academy of Pediatrics. Search dates: March 2, 2015, and October 1, 2015.

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